

CHEMICAL MIXTURES

Chemical Cocktails Are Mixed Pesticides More Potent?

Increasing evidence suggests that environmental chemicals that interact with the endocrine system harm the health of humans and animals. More recent studies suggest further that these chemicals act synergistically, meaning that their combined effect is greater than the sum of their individual effects. While few scientists doubt that endocrine disruptors can cause significant harm to humans and wildlife, there is a great deal of controversy over whether synergism is indeed part of the equation—and how researchers can go about finding out the truth of the matter.

In a paper published in the January–March 1999 issue of *Toxicology and Industrial Health*, Warren P. Porter, a professor of zoology at the University of Wisconsin in Madison, reported that mixtures of the pesticides aldicarb and atrazine and the fertilizer nitrate altered nervous system, endocrine, and immune system function in several strains of mice while each compound alone did not. In the study, mice were given drinking water laced with each of the eight possible combinations of the three chemicals in

concentrations approximating their maximum permissible concentration levels in groundwater. The researchers then examined aspects of behavior and physiology. The researchers distinguished between fall/winter and spring/summer experiments because the animals' hormones change with the seasons, which can affect metabolism of chemicals.

The most significant result involved the animals' ability to produce antibodies to foreign proteins. One group of mice exposed to aldicarb and nitrate during fall/winter had a tenfold increase in ability to make antibodies to foreign proteins. The increase in antibody production does not imply improved health, says Porter, because it may be occurring at the expense of some other aspect of immune function.

Unbound thyroxine (a thyroid hormone) increased by 25–50% in some of the treatment groups during spring/summer experiments, but the number of chemicals to which the mice were exposed made little difference in the results. "Thyroxine affects production of steroids in the adrenals; these can modify immune function," says Porter. Thyroxine can also have a profound impact on brain development. In behavioral experiments, most of the experiments resulted in suppressed aggression, although enhanced levels of aggression were also observed, he says.

There are two spiritual dangers in not owning a farm.

One is the danger of supposing that breakfast comes from the grocery, and the other that heat comes from the furnace.

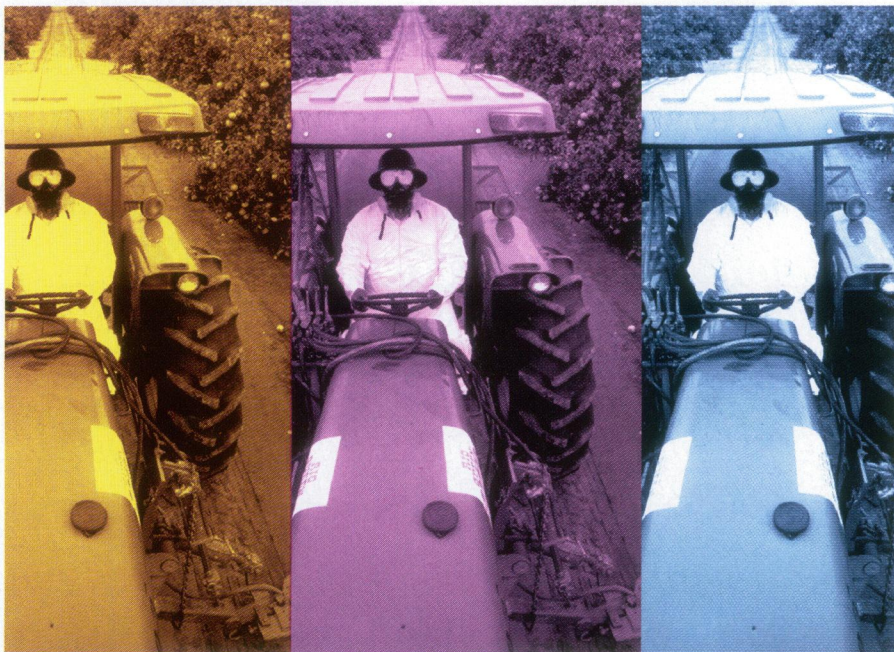
Aldo Leopold, *A Sand County Almanac*, 1949

A major implication of the study is that the U.S. chemical registration system has several shortcomings, says Porter. He points out there is virtually no testing of chemical mixtures, compounds are tested minus inert ingredients that go into commercial mixtures, end points include only cancer and mutations (but not immune, endocrine, nervous system, or development end points), and only single-exposure routes are used—a combination of oral, cutaneous, and respiratory routes is needed as well. Furthermore, he says, the tests do not include stresses from malnutrition, disease, or climate.

Ralph L. Cooper, chief of the Endocrinology Branch of the Reproductive Toxicology Division at the U.S. Environmental Protection Agency (EPA) National Health and Environmental Effects Research Laboratory, agrees that studies on chemical mixtures are lacking and emphasizes that the design of such studies creates special problems, particularly reproducibility. The difficulty of reproducing mixture studies is that when two variables (e.g., two chemicals) are combined, the amount of study work increases exponentially. "If you have four doses in one chemical, and four in the other, you end up with 16 treatment groups, so you have a large, cumbersome study," says Earl Gray, Jr., a research biologist with the EPA. "And four doses is often not enough to define the dose response. The interpretation requires some sophisticated statistical analyses."

Critics say Porter's results seem weak. Some point out that the differences between the spring/summer and fall/winter experiments were far greater than the differences between the treatment groups. "He ran a number of statistical tests, and only about 5% came out significant," says Cooper. "If the same set of experiments were done again, would a different 5% be significant? I couldn't get a sense of real synergy."

"We are dealing with very subtle responses in animals and possibly in people," says Porter, adding that the results may reflect different genetic vulnerabilities in some of the mice used in the study. Nonetheless, says Cooper, "The issues he raises are legitimate ones, and there is a ton of support in good peer-reviewed journal articles. The issue of developmental effects, sex differences, additivity, and the potential for synergism are all important questions in environmental toxicology." —David C. Holzman



Menacing mixtures? The synergistic effects of agricultural chemical mixtures on human health are controversial, and scientists agree that much more research on the issue is needed.